CHITOSAN, A NATURAL LIGAND FOR SUSTAINABLE AND ENVIRONMENTALLY BENIGN ASYMMETRIC TRANSFER HYDROGENATIONS

Vanessza Judit Kolcsár,[1,*] György Szőllősi[2]

[1]*Department of Organic Chemistry, University of Szeged, Dóm tér 8, Szeged, 6720, Hungary*
[2]*MTA-SZTE Stereochemistry Research Group, Dóm tér 8, Szeged, 6720, Hungary*
**Corresponding author: kolcsar.vanessza@chem.u-szeged.hu*

Abstract

The transfer hydrogenations are convinent methods of obtaining chiral alcohols by enantioselective catalytic reactions. Catalytic methods suit most of the environmental requirements, though most of the chiral catalysts are made of synthetic ligands and are used in organic solvent. Natural ligands have a great potential to meet more requirements particularly if the solvent could be changed to water-based mixtures.

We have studied the transfer hydrogenation of prochiral ketones catalyzed by an *in situ* prepared Ru-chitosan complex in aqueous media. The reaction of acetophenone and its substituted derivatives resulted in good enantioselectivities. Furthermore, to our delight in the reduction of several cyclic ketones over 90%, enantiomeric excesses were obtained, reaching up to 97% in the transfer hydrogenation of heterocyclic 4-chromanone or 4-thiochromanone derivatives. Based on these experiments, several N containing ketones were reduced in the above catalytic system. The results show that the position of the N atom and the number of its substituents influences the reached conversion and ee. Some of the N containing derivatives with the proper structure was transformed with high enantioselectivity (88-95%).

The pre-prepared Ru-chitosan complex provided identical results even after several months' storage without special precautions. With the comparison of the characterisation of the complex and the results of the transfer hydrogenations, we determined a possible complex and transition state structure. In conclusion the chiral catalyst prepared from a natural, inexpensive, readily available chiral ligand is a convenient alternative of the synthetic ligands and may be applied in environmentally friendly and sustainable processes for preparing optically pure chiral alcohols.

Introduction and aims

During the last few decades, the increased demand for optically pure fine chemicals accelerated the development of asymmetric catalytic procedures. Enantioselective transfer hydrogenations are among the most convenient methods for the preparation of optically pure compounds used as intermediates in the production of pharmaceuticals, agrochemicals, flavours and fragrances. For the transfer hydrogenation of various prochiral unsaturated compounds, a large variety of chiral complexes have been developed. Recent trends require environmentally friendly, sustainable processes, so the use of chiral ligands from natural sources became essential. With the deacetylation of chitin, chitosan can be obtained, which has multiple advantages. The biocompatible, biodegradable chitosan may replace the expensive chiral ligands. Due to the presence of the free amino groups in this biopolymer, it may be able to form complexes with metal cations [1]. Furthermore as a result of its hydrophilic character may be used in aqueous media. However, only few studies have been published attempting the use of chitosan complexes in asymmetric transfer hydrogenations and the results obtained until now are far behind the values produced using synthetic chiral ligands. With the use of chitosan derivatives, satisfactory results were obtained [2,3], however functionalization of the chiral polymer decreased the practical value of these procedures.

Our aim was to investigate the transfer hydrogenation of prochiral ketones catalyzed by a chiral Ru-chitosan complex prepared from unmodified, commercially available chitosan in aqueous solvents and to explore the applicability of this chiral complex. We also wanted to determine the structural requirements of the ketones, which are neccassary to obtain high optical purities. Examinations of the complex structure and that of the transition state during the reaction were also our primary tasks. As a final goal, we intended to develop a highly enantioselective, economic, environmentally friendly procedure for the convenient transfer hydrogenation of prochiral ketones.

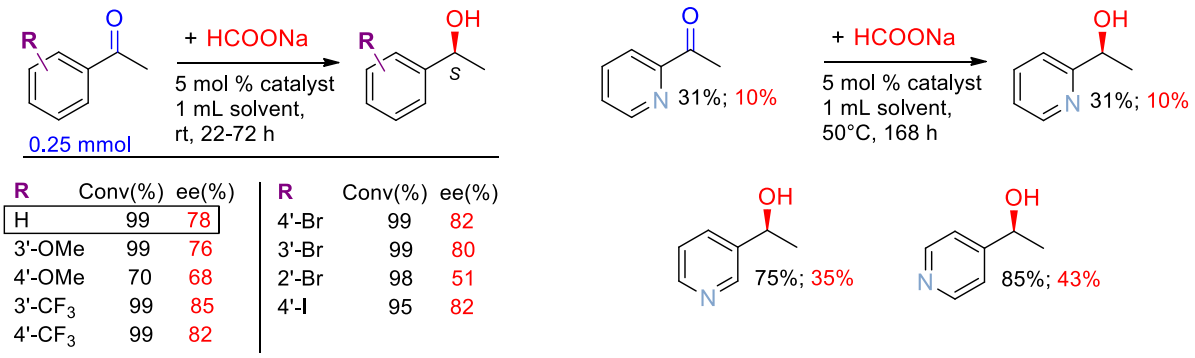
Experimental

The prochiral ketones, the hydrogen donors, the metal precursor and the chitosan were obtained from commercial sources and were used as received. Transfer hydrogenations were carried out in closed glass reactors. In a typical run, the metal precursor and chitosan were stirred in the solvent 30 min followed by addition of the hydrogen donor (HCOONa) and the prochiral ketone. The slurry was stirred for the desired time followed by extraction of the product three times with ethyl acetate. These products were analyzed by GC-MSD and GC-FID using chiral capillary column. For the characterization of the Ru-chitosan complex this was prepared *ex situ* and dried at room temperature. The product was used in SEM and IR spectroscopic investigations.

Results and discussion

First, the transfer hydrogenation of a few acetophenone derivatives was carried out in the new catalytic system. Optimization of the reaction conditions and the solvent composition led us to the conclusion that a water-iPrOH 4-1 solvent mixture provides the best enantioselectivities at room temperate. Although, acetylpyridine derivatives have similar structure as the acetophenones, the transfer hydrogenations of these compounds have not been examined before with catalyst bearing chitosan as the chiral ligand. Our experiments showed that the presence of the N in the aromatic ring has a detrimental effect on the conversion and the enantioselectivity, probably due to strong attachment of the ketone to the metal. The results of these experiments are summarized in Figure 1.

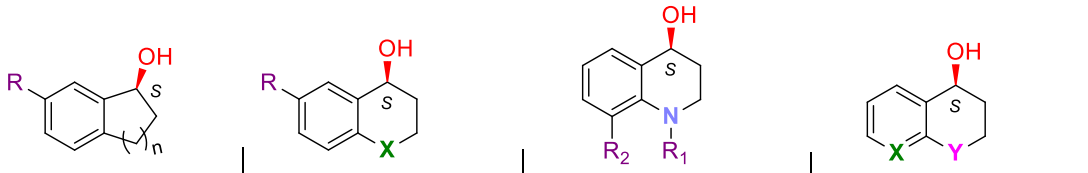
Figure 1. Enantioselective transfer hydrogenation of acetophenone and acetylpyridine derivatives with *in situ* formed Ru-chitosan complex.



Next, we examined the transfer hydrogenation of a large library of prochiral ketones with various structure under conditions found most appropriate in our previous experiments. The reduction of ketones having alicyclic ring connected to the aromatic group gave surprisingly high enantioselectivities, as shown in Figure 2. To our delight, results obtained in our

experiments exceeded the best values reported until now by the use of chitosan derivatives as a ligand. Moreover, the ketones including a heteroatom in the saturated ring, such as 4-chromanones and 4-thiochromanones provided the corresponding alcohols in even better, up to 97%, enantiomer excesses (Figure 2.) Based on these result the transfer hydrogenation of four N-containing ketones with similar structure was carried out. In most of the cases under the right reaction conditions the conversion and the ee approached the values achieved with 4-thiocromanone. As we mentioned before the N atom has a significant influence on the out-come of the reactions. If the N is hindered by a substituent, or by a bulky group in its surroundings the effect of the Ru-N bond will be weaker and the reactions take place faster with better enantioselectivities (Figure 2.). Encouraged by these results, we continued to explore the scope of this catalytic system, by attempting the asymmetric transfer hydrogenations of ketones having pyridyl ring condensed with a heterocyclic moiety. Based on the obtained conversions and ee values we suggest that the nitrogen found in the aromatic ring may strongly interact with the metal and with the chiral ligand as well. We also note that the steric effect of the six-membered cycloaliphatic ring still assured good ee's in these reactions, similarly with transformations of 4-(thio)chromanones.

Figure 2. Results of transfer hydrogenation of cyclic ketones with the Ru-chitosan catalyst.



n	Conv(%)	ee(%)
3	77	65
2	61	93
1	80	88
1	91	92 (R: CF_3)

X	R	Conv(%)	ee(%)
O	H	98	96
O	Cl	99	96
S	H	99	97
S	Cl	99	97
S	Me	91	96

R_1	R_2	Conv(%)	ee(%)
H	H	78	72
Boc	H	96	95
Br	H	97	88

X	Y	Conv(%)	ee(%)
N	S	99	94
N	N-CH_3	92	88

Further, we prepared the Ru-chitosan complex, which after slow evaporation of the solvent gave a dark orange film-like material (Figure 3.). This catalyst was equally efficient in the transfer hydrogenations as the *in situ* formed catalyst. The FT-IR spectrum of this material indicated the coordination of the Ru to the chitosan.

Based on the IR spectrums and the effect of the ketone structure on the conversion and enantioselectivity we suggested a plausible structure for the complex (Figure 3.). It is assumed that the amino groups of different glucosamine units are involved in the coordination of the Ru(II) ion. An outer-sphere mechanism is suggested, during which the ketones' six-membered ring assures the necessary rigidity to the molecule, whereas hydrogen-bond acceptor heteroatoms in the ring are able to interact with the hydroxyl groups of the chitosan improving the orientation of the ketone. Based on the above results we suggested the possible structure of the complex and the obtained high enantioselectivities were interpreted by stereospecific interactions of the prochiral compounds with the chitosan ligand.

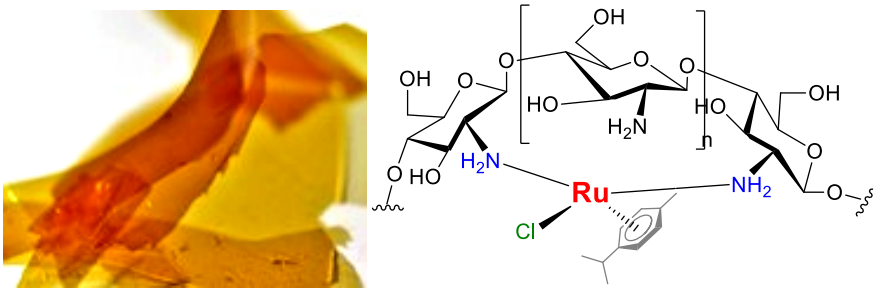


Figure 3. Photo and the probable structure of the *ex situ* prepared Ru-chitosan complex

Conclusions

In summary, we developed a sustainable and green method, using the biopolymer chitosan as a chiral ligand for the *in situ* formation of a Ru complex in aqueous catalytic system, in which high enantioselectivities were obtained in the asymmetric transfer hydrogenation of prochiral ketones. The enantiomeric excess values surpassed those reported in the literature obtained with chitosan derivatives. Acetophenone derivatives were reduced to the corresponding 1-arylethanols in up to 86% ee. The reactions of acetylpiridine derivatives were slower and gave lower ee values due to the stong bonding of the pyridyl N to the Ru. We obtained over 90% ee in the reaction of cyclic ketones, reaching up to 97% in the reduction of compounds having heteroatoms in the alicyclic ring. In the transfer hydrogenation of quinolinone derivatives high enantioselectivities were reached in case the amino group was protected or shielded by a nearby substituent. Further, we prepared *ex situ* the Ru-chitosan complex, which was equally efficient in transfer hydrogenations as the *in situ* formed catalyst. The FT-FIR spectrum of this material indicated the bonds established between the Ru cation and chitosan. Based on the above results we suggested the possible structure of the complex and the obtained high enantioselectivities were interpreted by stereospecific interactions of the prochiral compounds with the chitosan ligand. Finally, we mention that the highly selective chiral Ru complex was prepared using a cheap, natural material as chirality source, thus the developed method is a green, environmentally friendly and sustainable way to obtain optically enriched chiral alcohols.

Acknowledgements

Financial support by the UNKP-19-3-SZTE-153. New National Excellence Program of the Ministry of Human Capacities (V.J. Kolcsár) is appreciated.

References

[1] A. El Kadib, ChemSusChem, 8 (2015) 217.
[2] M. Babin, R. Clément, J. Gagnon, F.-G. Fontaine, New J. Chem. 36 (2012) 1548.
[3] B. Liu, H. Zhou, Y. Li, J. Wang, Chin. J. Org. Chem. 34 (2014) 2554.